REMARKS

Reconsideration of the allowability of the present application is respectfully requested.

Status of the Claims

Claims 54-56, 58-92, and 94-115 have been acted upon by the Examiner. No claims have been allowed. Claims 54, 76, 77, 79, 80, 82, 83, 86, 87, 90, 91, 111, and 112 have been amended. Claims 58 and 94 have been canceled. Claims 116-142 have been added. Accordingly, claims 54-56, 59-92, and 95-142 are presented for examination.

Claims 54, 76, 79, 82, 83, 86, 87, 90, and 111 have been amended to add the recitation "wherein the albumin solution subjected to cation exchange chromatography . . . has an albumin concentration of 10-250g.L^{-1}." Essentially, Applicants have added the recitation from dependent Claim 58 (Claim 94 contains the same recitation) to the independent claims 54, 76, 79, 82, 83, 86, 87, 90, and 111. Claims 58 and 94 were therefore canceled. Support for this amendment can be found in original Claim 25, and on page 6, lines 19-21 of the application as filed.

Claims 77, 80, 91, and 112 were amended to correct minor referencing errors.

Claims 116-133 are new dependent claims that add recitations to each preceding independent claim and relates to the albumin concentration subject to the negative mode cation exchange chromatography step of the preceding independent claims. Support for these claims can be found in original Claim 25, and on page 6, lines 19-21 of the application as filed.

Claims 134-142 are new independent claims that add the recitation "wherein the albumin solution subjected to cation exchange chromatography . . . contains glycosylated albumin and the glycosylated albumin is bound during the said cation exchange step." Essentially, Applicants have added the recitation from dependent Claim 55 (Claims 77, 80, 91, and 112 contain the same recitation) to the independent claims 54, 76, 79, 82, 83, 86, 87, 90, and 111 to create new independent Claims 134-142.

ARGUMENTS

A. 35 U.S.C. § 102(b) Rejections

The Examiner has rejected Claims 54, 56, 61, 64, 65, 74-76, 78, 79, 81, 90, 92, 96, 99, 100, 109-111, and 113-115 under 35 U.S.C. § 102(b) as being unpatentable over Fisher *et al.* (US 4,228,154) supported by Ohmura *et al.* (EP 0 570 916 A2).

Applicants have amended Claims 54, 76, 79, 82, 83, 86, 87, 90, and 111 to add the recitation "wherein the albumin solution subjected to cation exchange chromatography . . . has an albumin concentration of 10-250g.L^{-1}." Essentially, Applicants have added the recitation from dependent Claim 58 (Claim 94 contains the same recitation) to the independent claims 54, 76, 79, 90, and 111. Claims 56, 61, 64, 65, 74, 75, and 114 depend on Claim 54. Claim 78 depends on Claim 76. Claim 81 depends on Claim 79. Claims 92, 96, 99, 100, 109, 110, 115 depend on Claim 90. Claim 112 depends on Claim 111. Notably, the Examiner did not apply this §102(b) rejection to Claim 58 or Claim 94 in the Office Action dated March 10, 2005. Accordingly, since all the claims subject to this rejection contain the recitation that was previously recited in now canceled Claim 58 or Claim 94, this rejection is now moot.

Moreover, in order for a reference to anticipate a claim, each element found in the claim must be taught by the reference. The Examiner has explicitly conceded that Fisher *et al.* does not teach using an albumin concentration of 10-250 g/L, a recitation now found in each rejected claim. See paragraph 15(B) of Office Action. Accordingly, this rejection should be withdrawn with respect to Claims 54, 56, 61, 64, 65, 74-76, 78, 79, 81, 90, 92, 96, 99, 100, 109-111, and 113-115.

This rejection is also not applicable to the newly added claims. New Claims 116-133 are dependent on Claims 54, 76, 79, 82, 83, 86, 87, 90, or 111, and contain a further recitation regarding the albumin concentration subject to the cation exchange step. Thus, new Claims 116-133 are not anticipated by Fisher *et al.* for the same reasons as discussed above. New Claims 134-142 contain the recitation that is found in dependent Claims 55, 77, 80, 91, and 112. The Examiner has explicitly conceded that Fisher et al. does not teach an "initial albumin solution containing glycosylated albumin and the glycosylated albumin being bound during the cation exchange step." See paragraph 11(B) of Office Action. Accordingly, new Claims 134-142 are not anticipated by Fisher *et al.*

B. 35 U.S.C. §103(a) Rejections

The Examiner has presented several §103(a) rejections. Because previously pending Claims 54-56, 59-92, and 95-115 now incorporate the recitation of now canceled Claim 58 (or the corresponding Claim 94), these claims now include the recitation of negative mode cation exchange chromatography using an albumin solution having an albumin concentration of 10-250 $g.L^{-1}$. New Claims 116-133 also contain a recitation regarding the concentration of the albumin solution that is used in the cation exchange chromatography step. Accordingly, only the §103(a) rejection that was applied to Claims 58 and 94 is still applicable with respect to Claims 54-56, 59-92, and 95-115, and would be applicable to new Claims 116-133. Claims 134-142 have been added to include the limitations of Claim 55 (or corresponding Claims 77, 80, 91 and 112) in the independent Claims 54, 76, 79, 82, 83, 86, 87, 90, and 111. Accordingly, only the §103(a) rejection that was applied to Claims 55, 77, 80, 91 and 112 would be applicable to new Claims 134-142. Both of these rejections are addressed below.

With respect to these rejections, Applicants submit that the Examiner has not satisfied all of the three basic criteria required to establish a *prima facie* case of obviousness. MPEP §2143 states:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the publications themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or publications when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

In the arguments presented below, Applicants will demonstrate that there is no motivation to modify or combine the teachings of the references applied by the Examiner. Moreover, the teaching of the references if combined would not convey to one of ordinary skill in art a reasonable expectation of successfully purifying an albumin solution.

1. §103(a) Rejections That Would Be Applicable To Claims 54-56, 59-92, and 95-133

The Examiner rejected Claims 58 and 94 under 35 U.S.C. §103(a) as being unpatentable over Goodey *et al.* (WO 97/31947) in view of Fisher *et al.* (US 4,228,154), in further view of Curling ("Methods of Plasma Protein Fractionation," pp. 77-91, 1980). This was the only §103(a) rejection applied to Claims 58 and 94. Claims 54-56, 59-62, and 95-133 contain all of the recitations of now canceled Claims 58 or 94 (some of the claims have further recitations). Accordingly, since Claims 54-56, 59-92, and 95-133 contain all the recitations of now canceled Claims 58 or 94, this is the only §103(a) rejection that would be applicable to pending Claims 54-56, 59-92, and 95-133.

Applicants respectfully traverse this rejection.

(a) Discussion of Claimed Invention

The claimed invention came about as a result of the Applicants' further development of the albumin purification processes. The purification processes defined by the claims relate to end-stage "polishing" processes that can be applied to albumin that has already been partially purified in order to obtain even more highly purified albumin.

The applicants found that partially purified albumin could be further purified by exposure to cation and anion exchange steps, wherein the cation exchange step is run in the negative mode with respect to albumin. Unexpectedly, the applicants found that the negative mode cation exchange step operated more efficiently (*i.e.* allowed the recovery of more albumin and yet removed a greater proportion of impurities) when the albumin solution was highly concentrated.

These unexpected results are shown in the following table, which describes the result of applying different concentrations of an impure albumin solution to a cation exchange chromatography column operated in the negative mode with respect to albumin.

Load Concentration	Albumin yield %	Detected Contaminant Level %
5 $g.L^{-1}$	39	0.17
10 $g.L^{-1}$	53	0.15
25 $g.L^{-1}$	67	0.10

Thus, at higher load concentrations, negative mode cation exchange chromatography provides for more efficient recovery of albumin (albumin recovery increases from 39% to 67%). Moreover, at the same time, higher load concentrations result in impurities being more efficiently removed (contaminant levels reduced from 0.17% to 0.10%). See Declaration of Stephen Berezenko attached to this Reply.

This result was contrary to expectations. In a negative mode cation exchange step, the impurities in the albumin are bound to the cation exchange matrix, whereas albumin passes through without binding. As the concentration of the solution applied to the cation exchange matrix is increased (i.e. as the concentrations of both the albumin and the impurities in the applied solution increases) one would have expected that the cation exchange matrix would become less efficient due to increased demands being placed upon its capacity to bind and retain impurities.

In light of this result, it can be seen that the cation exchange step of the claimed processes is particularly suitable for end-stage "polishing" of a partially purified albumin solution because, at this stage of the purification process, albumin is typically provided at a high concentration.

Thus, the claims have been amended to reflect the key technical requirement to achieve increased purification efficacy, namely that the albumin solution should be significantly concentrated. Each of the pending claims now recite that the albumin solution applied to the negative mode cation exchange chromatography step should have a concentration of 10-250 $g.L^{-1}$.

None of the cited prior art addresses the issue of end-stage "polishing" of a partly purified albumin solution. In particular, none of the cited prior art suggests the combination of cation exchange chromatography run in the negative mode with respect to albumin for the treatment of an albumin solution that has a concentration of 10-250 $g.L^{-1}$.

(b) Discussion of the References

Goodey *et al.* Goodey *et al.* (WO 97/31947) describes *positive* mode cation exchange chromatography as *an initial step* of albumin purification. In other words, Goodey *et al.* suggests that cation exchange chromatography is useful as a crude separation step at the start

of an albumin purification process (for example, see the "preferred embodiment" of Goodey *et al.* at page 2, lines 14-28, which starts with positive mode cation exchange).

Goodey *et al.* does not indicate a preferred albumin concentration for application to the cation exchange step, as acknowledged by the Examiner in section 15(B) of the current office action.

Example 1 of Goodey *et al.* indicates that the albumin that was purified by cation exchange chromatography was produced in a cell culture at >1.5 $g.L^{-1}$ (page 15, line 8), although the culture was then diluted (page 15, lines 16-18) before filtration or centrifugation ("primary separation") to remove yeast cells (page 15, lines 23-27). Primary separation is said to lead to the loss of up to 25 % of the albumin (page 15, lines 27-29), although the loss can be minimised by resuspending the residual cell slurry in a further volume of water or buffer, repeating the primary separation step and collecting the thus produced albumin solution (page 16, lines 29-31). Thus, according to Goodey *et al.*, the initial albumin solution applied to a cation exchange step is one derived from a cell culture medium that contains albumin at a concentration of around 1.5 $g.L^{-1}$, which is diluted prior to primary separation, and then diluted again by repeat washing of the biomass in order to maximise albumin recovery.

The albumin solution is further conditioned by the addition of sodium octanoate and acetic acid in readiness for a first purification step of positive mode cation exchange chromatography (page 16, lines 5-13).

Accordingly, the teaching of Goodey *et al.* is to produce a *very dilute* albumin solution (most likely significantly below 1.5 $g.L^{-1}$, and certainly there is no suggestion of 10 $g.L^{-1}$) and to apply it to a cation exchange column that is *run in the positive mode* with respect to albumin, in order to achieve an *initial crude separation* of albumin from other contaminants.

Goodey *et al.* fails to suggest or make obvious the possibility of using cation exchange chromatography *run in the negative mode* with respect to albumin, using an albumin solution that has already been partially purified and thus has an *albumin concentration of 10-250 $g.L^{-1}$*, in order to "polish" that preparation.

Certainly, there is nothing in Goodey *et al.* to suggest that high albumin concentrations are the key to improving the efficacy of negative mode cation exchange chromatography.

Fisher *et al.* Fisher *et al.* (US 4,228,154) describes an albumin purification process involving cation and anion exchange steps run in the negative mode with respect to albumin.

Fisher *et al.* is directed to a process of purification of albumin "in the absence of process steps involving precipitation *or desorption* of the albumin" (see abstract of Fisher *et al.*; emphasis added). Fisher *et al.* emphasizes that the goal of their invention is to avoid process steps involving precipitation or desorption to decrease the likelihood of adverse changes in the native character of the albumin molecule:

> It is noteworthy, for example, that known ion exchange chromatographic methods for purification of albumin often involve multiple precipitation and resuspension steps similar to those extant in the cold alcohol fractionation processes and further involve multiple desorbtions of the albumin from the ion exchanger materials. Each such manipulation increases the potential for adverse changes in the native character of the albumin molecules.
>
> There exists, therefore, an ongoing need for new procedures which will efficiently isolate purified albumin from plasma while minimizing potential alterations in the native structure or character of the albumin or other plasma components.
>
> * * *
>
> According to the present invention, "chromatographically pure" plasma albumin is obtained in high yields by ion exchange chromatographic procedures which maintain the albumin in a solution phase throughout processing. (Column 1, line 63, to Column 2, line 17).

Maintenance of "albumin in a solution phase throughout processing" requires that the albumin never be bound to any resin. In other words, Fisher *et al.* requires that the albumin not enter the "solid-phase." Accordingly, Fisher *et al.* discloses purification of albumin using methods which do not require adsorption to either anion or cation resins. Example 1 of Fisher *et al.* discloses negative mode anionic exchange followed by negative mode cationic exchange. As all of the purification steps of Fisher *et al.* are "negative," use of Fisher *et al.* method ensures that albumin will never bind to a resin and be later eluted or desorbed from the resin. Thus, the methods of Fisher *et al.* do *not* require adsorption and desorption of

albumin from either cationic or anionic resins. Furthermore, Fisher *et al.* requires that *no desorption* occur. Indeed, the absence of desorption is the goal of Fisher *et al.*

Fisher *et al.* attaches no importance to the albumin concentration used in the negative cation exchange step. First, there is no teaching in Fisher *et al.* as to what concentration of albumin should be applied to the cation exchange chromatography column, as acknowledged by the Examiner in section 15(B) of the current office action. Second, Fisher *et al.* recommends that, prior to cation exchange, albumin solutions should be treated by gel-filtration to remove alcohol and salt from the albumin and that this can result in "*volume expansion of the albumin-containing fluids by 30-50%.*" (column 4, lines 50-57). Fisher is clearly unconcerned by the further dilution of its albumin solution prior to cation exchange. Accordingly, Fisher *et al.* fails to recognise that negative mode cation exchange chromatography of albumin solutions operates most efficiently when an albumin concentration of 10-250 $g.L^{-1}$ is used.

Curling Curling ("Methods of Plasma Protein Fractionation," pp. 77-91, 1980) has been cited by the Examiner as an incentive to use an albumin concentration of greater than 10 $g.L^{-1}$ in a negative mode cation exchange chromatography step.

Curling discusses the use of ion exchange procedures to purify albumin in section III, beginning on page 80. Curling suggests the use of ion exchange steps to purify albumin from "euglobin poor plasma" (see page 81, Fig. 2). Thus, Curling uses the method as a *crude* albumin purification procedure, rather than as a final "polishing" step.

Like Goodey *et al.*, Curling only discloses positive mode cation exchange chromatography. For example, Curling states that optimal conditions for anion exchange chromatography result in albumin being bound to, and then eluted from, the anion exchange column (page 80, section III, second paragraph). Curling teaches applying the albumin-containing product from the anion exchange step to a cation exchange column where "*under the above conditions albumin is bound,*" *i.e.* cation exchange *run in the positive mode* with respect to albumin (page 80-81, section III, third paragraph). Curling says nothing about the optimal loading of a *negative mode* cation exchange chromatography column, and there is nothing to suggest that conditions for optimal loading of a positive mode cation exchange step are directly applicable to the optimal loading of a negative mode cation exchange step.

There is absolutely no recognition in Curling that the purification of albumin by a *negative mode* cation exchange step can be optimised by loading with an albumin concentration of 10-250 $g.L^{-1}$.

(c) No Suggestion or Motivation to Combine References

The claims as amended are, in effect, equivalent to previous Claims 58 and 94, in that they are limited to the performance of negative mode cation exchange chromatography using an albumin solution having an albumin concentration of 10-250 $g.L^{-1}$. In paragraph 15 of the office action, the Examiner has rejected Claims 58 and 94 as obvious over Goodey *et al.*, in view of Fisher *et al.*, and further in view of Curling. The Examiner, however, has not provided evidence of a *prima facie* case of obviousness.

First, the Examiner has applied the teaching of Fisher *et al.* to the teaching of Goodey *et al.* as motivation to modify the positive mode cation exchange step of Goodey *et al.* so as to arrive at a negative mode cation exchange step as defined by the claims of the present application. There is no evidence of record, however, that would suggest to or motivate one skilled in the art to combine the disclosures of Goodey *et al.* and Fisher *et al.* Goodey *et al.* discloses positive cation exchange. Fisher *et al.* discloses negative cation exchange and negative anion exchange with the goal that desorption of albumin is to be avoided.

The abstract of Fisher *et al.* states, "Purified plasma albumin is obtained by ion exchange chromatographic procedures and in the absence of process steps involving precipitation or desorption of the albumin." Column 2, lines 36 to 38, of Fisher *et al.* state: "At no point in the process of the invention is the albumin precipitated or removed from the solution phase." Accordingly, the goal of Fisher *et al.* is to develop a process for purifying albumin that would neither result in removal of the albumin from the solution phase nor require desorption to re-enter the solution phase.

In stark contrast, Goodey *et al.* discloses positive cation exchange, which requires binding to a solid resin followed by desorption. Accordingly, the teachings of Goodey *et al.* are in direct conflict with Fisher *et al.* MPEP §2143.01 states:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants submit that to use the invention of Fisher *et al.* in conjunction with Goodey *et al.* would constitute a modification of Fisher *et al.* which is unsatisfactory for its intended purpose. Accordingly, the Examiner's combination of Goodey *et al.* and Fisher *et al.* is invalid because the criteria that a suggestion or motivation to modify the teachings of the publications or to combine the publication teachings has *not* been met.

MPEP §2141 states (emphasis added), "The references must be considered *as a whole* and must suggest the desirability and thus the obviousness of making the *combination.*" In considering Fisher *et al.* in its entirety, it is clear that Fisher *et al.* not only directly conflicts with Goodey *et al.*, it teaches away from Goodey *et al.* and the claimed invention.

Applicants respectfully submit that the present obviousness rejection is based on a hindsight reconstruction of the present invention. The Examiner has presented no objective evidence that, without the present application to use as a guide, one of skill in the art would, upon reviewing Goodey *et al.* and Fisher *et al.*, have selectively ignored those portions of Fisher *et al.* that are in conflict with Goodey *et al.* Without the present application, one of ordinary skill in the art would have no basis to selectively ignore those conflicting portions of Fisher *et al.*

The Examiner, in paragraph 5(A) of the current office action, argues that Fisher *et al.* merely states that such desorption or precipitation of albumin "increases the potential for adverse changes in the native character of the albumin molecule." Therefore, according to the Examiner, Fisher *et al.* does not require that albumin be purified with no desorption steps, and it does not mean that albumin purified using such steps will be adversely affected. Even if this is the correct interpretation of Fisher et al, the Examiner is respectfully missing the point. The issue is not whether Fisher *et al.* absolutely precludes using a desorption step, e.g. a cation exchange step in the positive mode, but rather whether one of skill in the art would in applying Fisher *et al.* look to references that use desorption steps. They would not. In fact, the very next sentence in Fisher *et al.* after the one quoted by the Examiner states that there exists "an ongoing need for new procedures which will efficiently isolate purified albumin from plasma while minimizing potential alterations in the native structure or character of the albumin . . ." Since the goal of Fisher *et al.* is to minimize alterations in the native structure

of albumin, one of skill in the art applying Fisher *et al.* would not look to references that could potentially use purification steps that could introduce alterations, *e.g.*, Goodey *et al.*

Second, even if one were to accept that Fisher *et al.* can be used as motivation for the change in mode of cation exchange chromatography from positive to negative (which we do not) then, as discussed in more detail below, it is clear that the Examiner's reliance on Curling for further process details is improper.

To the extent that Curling says anything about optimal column loading at all (which, as discussed above, is most unclear), then it only teaches optimal column loading in respect to *positive mode* cation exchange chromatography. If one of skill in the art has taken the teaching of Fisher *et al.* into account as motivation to modify the teaching of Goodey *et al.* so as to use negative rather than positive mode cation exchange chromatography, then there is no reason for the skilled person to consult references that are solely concerned with loading positive mode cation exchange columns (such as Curling). Thus, if one of skill in the art took Fisher *et al.* into account when designing a purification process, they would not consult Curling, because *Curling says nothing about negative mode cation exchange chromatography*. In fact, Fisher warns the reader to avoid any positive mode process steps, i.e. process step that causes binding of albumin. "*At no point in the process of the invention is the albumin to be precipitated or removed from the solution phase.*" (Column 2, lines 36-38).

Likewise, Curling warns its readers that cation exchange chromatography should be conducted *exclusively in the positive mode* with respect to albumin. "*In chromatography on CM-sepharose* [i.e. cation exchange chromatography], *albumin is eluted in fraction 2 (Fig. 4). It was found* ***necessary to bind albumin*** *at this stage in order to eliminate pigmented material in fraction 1.*" (Page 82, first paragraph) (emphasis added). If the skilled person did modify the teaching of Fisher *et al.* in light of Curling, then they would do so by importing the cation exchange method of Curling *in toto*. In doing so, it is clear that the modified process would be one that resulted in the use of *positive mode* cation exchange chromatography. In other words, Curling teaches away from the present invention.

Since Curling relates exclusively to positive mode ion exchange method (*i.e.* a method in which it is said to be necessary to bind albumin), its teaching is of the type that Fisher *et al.* specifically tells its readers to avoid (*i.e.* Fisher *et al.* tells its reader to avoid a

process that removes albumin from the liquid phase). The teachings of Fisher *et al.* and Curling, at least insofar as they concern the purification of albumin by cation exchange chromatography, are clearly incompatible. MPEP §2141 specifically warns against combining such references where the references considered "as a whole" do not suggest the desirability of making the combination. Accordingly, the skilled person, starting from the teaching of Fisher *et al.*, would not consult Curling.

In any case, even if the skilled person did consult Curling, the teaching of the combined references would not convey to one of ordinary skill in art a reasonable expectation of successfully purifying an albumin solution. The MPEP §2143 requires that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

There is nothing in the Fisher *et al.* or Curling that would suggest to one of skill in the art that the optimal loading conditions given for positive mode cation exchange chromatography would be applicable to negative mode cation exchange chromatography. With positive mode cation exchange you are trying to bind your protein of interest and minimize the binding of contaminants, whereas with negative mode cation exchange this is reversed. Different technical considerations apply to these different modes. For example, with positive mode cation exchange, separation of the protein of interest from contaminants is achieved via three stages: loading, washing, and eluting. In negative mode cation exchange, separation is only based on how the column is loaded. Moreover, the pH and the conductivity of the chromatography solutions would be different. It is implausible that one of skill in the art would take a process detail from the description of positive mode cation exchange chromatography in Curling and apply it, *in isolation from other aspects of Curling's method* of positive mode cation exchange chromatography, to the negative mode cation exchange chromatography method of Fisher *et al.*

In fact, all of Goodey *et al.*, Fisher *et al.* and Curling fail to provide an indication that the efficacy of an albumin purification process using cation exchange chromatography that is run in the negative mode with respect to albumin can be optimised by using an albumin concentration in the range of 10-250 $g.L^{-1}$. None of Goodey *et al.*, Fisher *et al.* and Curling

suggest that the applicants' surprising result (i.e. that higher albumin concentrations lead to increased removal of contaminant) could have been obtained.

In view of the above, Applicants respectfully request that the only remaining applicable 35 U.S.C. §103(a) rejection of Claims 54-56, 59-92, and 95-115 over Goodey *et al.* in view of Fisher *et al.*, and further in view of Curling be withdrawn.

2. §103(a) Rejections That Would Be Applicable To Claims 134-142

The Examiner rejected Claims 55, 77, 80, and 91 under 35 U.S.C. §103(a) as being unpatentable over Fisher *et al.* (US 4,228,154) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-17, 1984). This was the only §103(a) rejection applied to Claims 55, 77, 80, and 91 Claims 134-142 contain all of the recitations of previously pending Claim 55, 77, 80 or 91(some of the claims have further recitations). Accordingly, since Claims 134-142 contain all the recitations of previously pending Claims 55, 77, 80, and 91, this is the only §103(a) rejection that would be applicable to new Claims 134-142.

Applicants respectfully traverse this rejection.

(a) Discussion of Claimed Invention

In the course of the development of the present invention, the Applicants unexpectedly found that cation exchange chromatography that is run in the negative mode with respect to albumin could be used to separate non-glycosylated albumin from glycosylated albumin. Glycosylated albumin is an undesirable contaminant.

This is shown in the following table, in which a 50 $g.L^{-1}$ albumin solution was exposed to cation exchange ("CE") chromatography run in the negative mode with respect to albumin. See Declaration of Stephen Berezenko attached to this Reply.

Glycosylated albumin content	
Before CE treatment	After CE treatment
0.2%	0.07%

Claims 134-142 have been added along with previously pending Claims 55, 77, 80, 91 and 112 to reflect this finding, and now specify that the albumin that is subjected to the

negative mode cation exchange step contains glycosylated albumin and that the glycosylated albumin is bound during the cation exchange step.

(b) Discussion of the References

Fisher *et al.* Fisher *et al.* (US 4,228,154) discloses negative cation exchange and negative anion exchange with the goal that desorption of albumin is to be avoided. Fisher et al. says nothing regarding separating glycolsylated albumin from non-glycosylated albumin. In paragraph 11(B) of the current office action, the Examiner has accepted that Fisher *et al.*, does not teach the separation of glycosylated albumin from non-glycosylated albumin in the cation exchange step.

Shaklai *et al.* The examiner correctly reviews the technical content of Shaklai *et al* in section 11(C) of the current office action. Shaklai *et al.* discloses that Plasma-derived albumin can be up to 10% (non-enzymatically) glycosylated and that glycosylated albumin can be separated from non-glycosylated albumin by GlycoGel B affinity chromatography.

Shaklai *et al* says nothing about the separation of glycosylated albumin from non-glycosylated albumin *using cation exchange chromatography*. Shaklai *et al* teaches that glycosylated albumin can be separated from non-glycosylated albumin by GlycoGel B affinity chromatography. GlycoGel B affinity chromatography *is not the same* as cation exchange chromatography. As its name implies, GlycoGel B is an affinity matrix with a specific affinity for glycosylated proteins, and it does not function as an ion exchange medium.

(c) No Suggestion or Motivation to Combine References

New Claims 134-142 are, in effect, equivalent to previously pending Claims 55, 77, 80, 91 and 112 in that they recite "wherein the albumin solution subjected to cation exchange chromatography . . . contains glycosylated albumin and the glycosylated albumin is bound during the said cation exchange step." In paragraph 11 of the office action, the Examiner has rejected Claims 55, 77, 80, 91, and 112 as obvious over Fisher *et al.*, and Shaklai *et al.* The Examiner, however, has not provided evidence of a *prima facie* case of obviousness.

First, the Examiner appears to have incorrectly applied the teaching of Shaklai *et al.* to the questions of obviousness. The Examiner states that Shaklai *et al.* makes obvious those

claims that are directed to a process of purifying albumin in which the albumin that is subjected to the *negative mode cation exchange* step contains glycosylated albumin and that the glycosylated albumin is bound *during the cation exchange step*. The sole teaching of Shaklai *et al.*, however, is that glycosylated albumin can be separated from non-glycosylated albumin by GlycoGel B *affinity* chromatography.

GlycoGel B affinity chromatography *is not the same* as cation exchange chromatography. As its name implies, GlycoGel B is an affinity matrix with a specific affinity for glycosylated proteins, and it does not function as an ion exchange medium. Shaklai *et al* says nothing about the separation of glycosylated albumin from non-glycosylated albumin *using cation exchange chromatography*.

The only disclosure of cation exchange chromatography in Shaklai *et al* is discussed in the legend to Fig. 1 (page 3813) in which Shaklai *et al* use cation exchange chromatography to separate different glycosylated tryptic peptides (non-glycosylated peptides having previously been removed using boronic acid affinity chromatography (*i.e.* GlycoGel B)). Thus, Shaklai *et al* teaches the reader that cation exchange chromatography can be used to separate one glycosylated peptide from a different glycosylated peptide. This is *not* an indication, however, that cation exchange chromatography can be used to separate a non-glycosylated protein from an otherwise identical glycosylated version of the same protein.

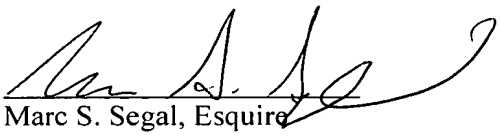
Thus, even if the skilled person consulted the teaching of Shaklai *et al.*, with the intention of removing glycosylated albumin, then there is no reason for the skilled person to think that glycosylated albumin could be separated from non-glycosylated albumin using a negative mode cation exchange chromatography step. Accordingly, new Claims 134-142 are not obvious over Fisher *et al.* in view of Shaklai *et al.*

In view of the above, Applicants respectfully submit that new Claims 134-142 are patentable over Fisher *et al.* in view of Shaklai *et al.*

Accordingly, Applicants respectfully submit that the application has been placed in a condition for allowance.

The Commissioner is authorized hereby to charge any fees or credit any overpayment associated with this Reply (copy enclosed) to Deposit Account Number 19-5425.

Respectfully submitted,



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